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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/671,253	09/25/2003	Stephen L. Archer	3241-P03287US01	8152

110 7590 07/29/2005

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1601 MARKET STREET
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PHILADELPHIA, PA 19103-2307

EXAMINER

KAUSHAL, SUMESH

ART UNIT PAPER NUMBER

1633

DATE MAILED: 07/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/671,253

Applicant(s)

ARCHER ET AL.

Examiner

Sumesh Kaushal Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 April 2005.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1-12 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☒ The drawing(s) filed on 20 February 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 4/20/05.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

J. J. W.

DETAILED ACTION

Applicant's response filed on 04/20/05 has been acknowledged.

Claims 1-12 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-4 and 6-8 rejected under 35 U.S.C. 102(b) as being anticipated by Nuss et al Gene Therapy 3:900-912, 1996).

The scope of invention as claimed encompasses an expression vector encoding a K⁺ channel gene and a transformed host cell.

The cited art teaches reversal of potassium channel deficiency in cells from failing hearts. The cited art further teaches a replication defective adenoviral vector encoding a K⁺ channel gene. The cited art further teaches transduction of cardiac myocytes, using the adenoviral vector encoding the *Shaker B* a K⁺ channel gene (page 900, col.2, para.2; page 901 col.1 and 2, page 911, col.1, para. 3). Thus the cited art clearly anticipate the invention as claimed.

Claims 1-4 and 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Humes et al (Cir. Res. 85:489-497, 1999, *ref of record PTO-1449*).

The scope of invention as claimed encompasses an expression vector encoding a K⁺ channel gene and a transformed host cell.

Humes et al teaches K⁺ channel genes encoding Kv1.5 and Kv2.1/9.3, Kv1.2, Kv3.1 and stable transfection of host cells using the expression vectors which is replication deficient in mouse host cells (page 489 abstract, page 490 col.1 para.4; pages 491-494). Thus the cited art clearly anticipate the invention as claimed.

Claims 1-4 and 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Ling et al (J Biol Chem.275(39):30683-9, 2000).

Ling teaches K⁺ channel genes encoding large conductance calcium-sensitive K⁺ channel genes and BK_{Ca} and stable transfection of host cells using the expression vectors which is replication deficient in host cells (page 30683, abstract; page 30685 col.2 para. 2, fig-2, fig-3). Thus the cited art clearly anticipate the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nuss et al Gene Therapy 3:900-912, 1996 as applied to claims 1, 3-4 and 6-8 above, and further in view of Hammond et al (US 6100242, 2000).

The teaching of Nuss et al is described above. Even though Nuss teaches a replication-deficient adenoviral vector encoding a K⁺ channel gene, the cited art does not teach the use of a tissue specific promoter.

Hammond teaches method for increasing contractile function in the heart of a patient by administering to the myocardial cells a replication-deficient adenovirus wherein the expression of a transgene encoding an angiogenic protein is under the control of a tissue-specific promoter (col. 21, lines 35-42, lines 65-67).

Thus it would have been obvious to one ordinary skilled in the art at the time the instant invention was made to modify the adenovirus vector as disclosed by Nuss by substituting the CMV promoter with a tissue-specific promoter in view of Hammond. One would have been motivated to do so to regulate the gene expression in a tissue of interest. One would have a reasonable expectation of success, since substitution of a promoter with a promoter of interest been routine in the art at time the instant invention was made. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

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art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating pulmonary hypertension by administering to person a replication-deficient adenovirus vector encoding the Kv1.5 gene, wherein the vector is administered by intratracheal nebulaziation, does not reasonably provide enablement for a method of treating all vascular diseases using any and all viral or non-viral expression vectors encoding any K⁺ channel gene, wherein the vector is administered via any and all route of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature Of Invention:

The instant invention relates to a method of treating any vascular disease via method of K⁺ channel gene therapy.

Breadth Of Claims And Guidance Provided By The Inventor:

The scope of invention as claimed encompasses method of treating any vascular disease by administering to a person any viral or non-viral vector via any and all routes of administration (oral, nasal, systemic, local, nabulization) encoding any K⁺ channel gene. At best the specification teaches that administration of a replication-deficient adenovirus vector encoding the Kv1.5 gene via intratracheal nebulaziation results in the expression of Kv1.5 in the lungs of chronic hypoxic rats, which results in reduced pulmonary hypertension (see Spec. Fig-1-3; para 0076, example-2). Besides reducing the pulmonary hypertension via administering an adenoviral vector encoding the Kv1.5

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gene directly to the affected lungs the specification as filed fails to disclose that the administration of any other K⁺ channel gene results in the treatment of pulmonary hypertension and/or patent-ductus-arteriosus and/or any other vascular disease. Thus it would require an undue amount of experimentation to practice the invention as claimed.

State Of Art And Predictability:

The scope of the instant invention encompasses genetic modification of a cell in-vivo, therefore the invention falls in the realm of gene therapy. The gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy (see Juengst BMJ, 326:1410-11, 2003; Check NATURE 422:7, 2003; Couzin et al, SCIENCE 307:1028, 2005; Rosenberg et al, SCIENCE 287:1751, 2000; Anderson, NATURE 392:25-30, 1998; Touchette, NAT. MED. 2(1) 7-8, 1996). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success. The advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease.

In instant case pulmonary arterial hypertension (PAH) is a disease of the pulmonary vasculature, defined by an elevated pulmonary vascular resistance (PVR),

which eventually leads to right heart failure and premature death. The cause remains unknown, and available treatments are limited, expensive, and often associated with significant side effects. In PAH, the pulmonary arteries (PAs) manifest pathological proliferative vascular remodeling that includes cellular proliferation in both the intima and the media and muscularization of the normally thin-walled distal PAs. Endothelial dysfunction results in an increase in the ratio of endothelial-derived vasoconstrictors to vasodilators. While vasoconstriction contributes, especially early in PAH, the obstructive vascular remodeling is the major cause of the elevated PVR and ultimately the right heart failure. The development of PAH is complex (Sweeney et al *Respir Res* 1:40-48, 2000). The pulmonary circulation is very different from the systemic circulation; for example, the pulmonary circulation has low pressure compared with the systemic circulation and constricts to hypoxia, while the systemic circulation dilates. This difference might be in part due to the fact that PASMC mitochondria, important oxygen sensors, are different from the systemic arterial SMC mitochondria. Furthermore several abnormalities that have been described in PAH that contributes to a resistance to apoptosis and a proliferation/apoptosis imbalance within the vascular wall. In a subset of PAH patients, germ-line and acquired loss-of-function mutations have been described in bone morphogenetic protein receptor 2 (BMPR2). Activation of the BMPR2 axis leads to suppression of proliferation and activation of apoptosis in normal PA SMCs (PASMCs) but not in PASMCs from patients with PAH. Furthermore gene microarray studies show that in patients with PAH, there is dysregulation of mediators of apoptosis in the PA wall that favors suppression of apoptosis. For example, bcl-2 is upregulated in

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PAH. In addition, specific PASMC voltage-gated K⁺ (Kv) channels, such as Kv1.5, are down regulated in both animal models and human PAH (see McMurtry et al, J Clin Invest. 115(6):1479-91, 2005). Thus considering the limited amount of guidance provided in the instant specification and the complexities found in the state of the pulmonary hypertension art, it is highly unpredictable that one skilled in the art would use the invention as claimed to treat any vascular disease (atherosclerosis, varicose veins, any heart abnormality, aneurysm, hypertension etc) without further undue amount of experimentation.

Furthermore, it has been difficult to predict the efficiency and outcome of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors. Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. On the other hand vector comprising DNA viruses and liposome coated DNA have been used to transduce non dividing cells but this results in a transient expression due to non-integration of transgenes in host cells. In addition, the use of adenoviral and adeno associated viral vector is also problematic because these vectors elicits considerable immune response in vivo, which affects the sustained expression of the transduced genes. Furthermore, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going

rapid cell division, which is quite not the case in-vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacles to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets. In addition there exists an uncertainty about the degree to which a vector's genetic material may integrate into the host genome extends to most types of gene therapy trials. Scientists are also unsure how an insertion could affect a patient, and worry cancer could occasionally be triggered, such as occurred various trials involving gene therapy (see Check Nature 422:7, 2003). Although, the gene therapy holds much promise to come, the success will only be achieved through continued rigorous research on the most fundamental mechanisms that contribute to a genetic disease along with the pathogenesis of the disease, gene delivery and gene expression in animals.

In instant case treating any or all vascular diseases by administering any and all viral or non-viral expression vectors encoding any K⁺ channel gene, wherein the vector is administered via any and all route of administration is not considered routine in the art and without sufficient guidance to a specific vascular disease and a therapeutic potential of a gene in context the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991).

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Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547**. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**.

Sumesh Kaushal
Examiner GAU 1636


SUMESH KAUSHAL
PATENT EXAMINER